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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,766	07/12/2001	Avi Ashkenazi	10466/70	4054

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EXAMINER	
KEMMERER, ELIZABETH	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/904,766	**Applicant(s)** ASHKENAZI ET AL.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *01 May 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *44-46 and 49-52*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

ATTACHMENT TO ADVISORY ACTION

11. NOTE: The rejections are maintained. HOWEVER, upon further consideration, the examiner no longer asserts that mRNA levels are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., Greenbaum et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., King et al., Bork et al., Madoz-Gurpide et al. The following references cited by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Zhigang et al., Meric et al., Wang et al., Munaut et al., Celis et al., Maruyama et al., Rudlowski et al. The basis of the maintained rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. This issue has been thoroughly addressed on the record both by the examiner and Applicant.

Applicant's arguments pertaining to the remaining issue (after final response, 01 May 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicant relies on Orntoft et al., Hyman et al., and Pollack et al. as evidence that gene amplification increases mRNA expression in general. Applicant criticizes Pennica et al. and Konopka et al. as allegedly failing to establish that it is more likely than not that gene amplification does not correlate with increased mRNA production.

Specifically, regarding Orntoft et al., Hyman et al., and Pollack et al., these references have been extensively discussed on the record. The evidence has been

considered anew, and the examiner maintains her positions regarding these pieces of evidence. The preponderance of the evidence supports maintaining the rejections.

Regarding Pennica et al., Applicant argues that Pennica et al. is limited to certain WISP genes and says nothing to whether or not gene amplification correlates with increased mRNA production in general. Similarly, Applicant argues that Konopka et al. is limited to the ***abl*** gene and does not speak to whether or not gene amplification correlates with increased mRNA levels in general. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. each provide specific examples of gene amplification events in tumors that did not correlate with increased mRNA levels. Similarly, Konopka et al. provides an example of gene amplification not correlating with increased protein expression. Another important example of a lack of correlation between gene amplification and mRNA/protein overexpression is provided by Hanna and Mornin, who teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Hanna and Mornin support the rejection, in that Hanna and Mornin show that gene amplification does not reliably correlate with protein over-expression, and thus the level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed proteins is not in currently

available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The general concept of gene amplification's lack of correlation with mRNA/protein overexpression was addressed with reference to Sen in the Office Action mailed 02 June 2003. Specifically, cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Furthermore, Godbout et al. speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, **a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified**." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to

ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence that PRO269 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006 (of record). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that *it is more likely than not that gene amplification does NOT correlate with increased protein levels*, absent evidenec

that the protein has biological relevance in cancer. There is no such evidene for PRO269.

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Hanna and Mornin, Sen, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

At p. 10 of the response, Applicant argues that the examiner is incorrect when stating that the specification has not identified anything rare or anything in common among the lung tumor samples in which the PRO269 gene is amplified. Applicant argues that PRO269 is overexpressed in certain lung tumors but not in any colon tumors, and is thus a lung cancer marker. Applicant further urges that there is no legal requirement that PRO269 be able to distinguish between different types of lung cancers. This has been fully considered but is not found to be persuasive. The examiner's comments are taken out of context. In the amendment of 22 August 2006, Applicant argued that they are not required to establish overexpression in a majority of tumors. Applicant urged that markers for rare tumors are valuable. Finally, Applicant argued that they have shown an overexpression in lung tumors but not colon tumors, which is useful. The examiner responded as follows:

> The specification does not disclose a rare type of tumor that can be diagnosed with PRO269 biological molecules. If a skilled artisan used a PRO269 genomic DNA probe on a new lung sample and there was no amplification, no diagnosis could be made since PRO269 was amplified in some known lung tumors and not amplified in other known lung tumors. The specification asserts that PRO269 polypeptides are elevated in tumor tissues based on gene amplification results; however, the literature evidences that this assumption is a false one. The claims are directed to PRO269 antibodies which can only detect differences in protein levels. As argued on the record, the gene amplification data for PRO269 genomic DNA do not impart utility to the PRO269 polypeptides or antibodies because amplification of DNA is not predictive of increased mRNA levels and increased polypeptide levels. Regarding rare tumor markers, such rare tumor markers are only useful if the type of rare tumor it identifies is known. The specification has not identified anything rare, or anything in common, among the

> lung tumor samples in which the PRO269 gene is amplified. PRO269 gene tested positive in LT7, LT13, LT9, LT12, LT11, LT15, LT17, and LT19 samples. Table 8 identifies these samples as lung squamous cell carcinomas, adenocarcinomas, and mixed tumors of various stages.

The examiner maintains this position.

Beginning at p. 11 of the response, and at other places in the response as well, Applicant refers to the Goddard declaration, Orntoft et al., and Pollack et al. These pieces of evidence have been thoroughly addressed on the record. They have been considered anew again, and the examiner maintains her previous position regarding these pieces of evidence. The preponderance of the evidence supports maintaining the rejections.

At p. 26, Applicant discusses the Godbout et al. and Bea et al. references. Applicant urges that these references, along with Orntoft et al., Hyman et al., and Pollack et al., constitute evidence that gene amplification generally correlates with mRNA/protein overexpression. This has been fully considered but is not found to be persuasive. Godbout et al. is discussed above. Regarding Bea et al., it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased protein expression. PRO269 is not a putative oncogene, and the function of the encoded protein is not known. Regarding Orntoft et al., Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and

polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO269 in the instant specification. That is, it is not clear whether or not PRO269 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any, of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO269 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

At p. 27, Applicant refers to the Li et al. paper. Applicant urges that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Applicant refers to the supplemental information accompanying the Li et al. article, enclosed as Exhibit A.

Applicant urges that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. Hyman et al. and Pollack et al. are not considered detrimental to the instant rejections, as discussed above. Therefore, the preponderance of the totality of the evidence, considered anew, supports maintenance of the rejections.

It is believed that all pertinent rejections have been addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

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